Retinoids and Cancer

The synthetic retinoids represent a new class of drugs which are highly effective in the treatment of a broad spectrum of dermatologic disease, including cystic acne, psoriasis, and cutaneous disorders of keratinization [1–3]. Moreover, the use of synthetic retinoids in cancer prevention and therapy for both cutaneous and internal tumors is potentially the most significant clinical use of these drugs.

Vitamin A deficiency may provide a conceptual link in understanding how retinoids may be effective as therapy for benign dermatoses and be of value in the treatment and prevention of skin cancer. One characteristic feature of vitamin A deficiency is a squamous metaplasia of a variety of epithelia, including the trachea, cornea, urinary bladder, parotid gland, prostate, and uterine cervix [4]. Increased cell proliferation and hyperkeratosis are features of both squamous metaplasia and some benign dermatoses, for example, psoriasis. Similarly, follicular hyperkeratosis is seen both in vitamin A deficiency and in acne, keratosis follicularis and pityriasis rubra pilaris.

The finding that retinoids rapidly reverse the squamous metaplasias induced by both vitamin A deficiency and by carcinogens supports the concept that retinoids may be of value in cancer chemoprophylaxis. Furthermore, vitamin A deficiency may be a precancerous disease. For example, vitamin A deficiency in the rat enhances the susceptibility of the respiratory tract, bladder, and colon to experimental carcinogenesis. In humans, epidemiologic studies have associated the incidence of cancer with decreased serum retinol [5].

During the past 10 years, in practical demonstration of the above concept, several retinoids have been used in animals and humans in the treatment or prevention of skin tumors. Initially, tretinoin (all-trans-retinoic acid) was used both topically and systemically. More recently, isotretinoin (13-cis-retinoic acid) and aromatic derivatives of retinoic acid (etretinate) and retinoid benzoic acid derivatives (arotinoids) have been demonstrated to be more effective and less toxic than tretinoin in the treatment of skin diseases, including tumors [1–3,6].

Moon and Itti suggest that there are several areas where retinoids may prove useful in clinical oncology: (1) for treatment of advanced disease, (2) for treatment which is adjuvant to other anticancer therapy, (3) for reversal or differentiation of preneoplastic lesions, (4) for prevention of cancer in high-risk populations, and (5) for the prevention of cancer in the general population [7].

The synthetic retinoids, isotretinoin and etretinate, have been used in the treatment and prevention of cutaneous malignancy in patients with multiple basal cell carcinomas due to chronic sunlight exposure, the nevoid basal cell carcinoma syndrome, or xeroderma pigmentosum; multiple actinic keratoses; multiple keratoacanthomas (Ferguson-Smith); solitary large keratoacanthomas; porokeratosis of Mibelli with malignant degeneration (squamous cell carcinoma, Bowen’s disease); malignant eccrine poroma; epidermodysplasia verruciformis; oral leukoplakia; cutaneous metastases of malignant melanoma and cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome) [1,2,6]. Aside from the actinic keratoses, the solitary keratoacanthomas, and approximately 10% of basal cell carcinomas, the synthetic retinoids usually do not cure cutaneous tumors but do produce variable degrees of partial regression when given at high dosage.

Precancerous diseases in organs other than the skin also have been reported to respond to retinoids. Two placebo-con-
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For example, retinoids promote differentiation of embryonal carcinoma undifferentiated stem cells into stable, non-neoplastic differentiated cells. The HL-60 human promyelocytic leukemia cell line is similarly induced to terminal benign differentiation with retinoids, as the c-myc oncogene is being suppressed. Retinoids also inhibit proliferation of malignant cell lines with accumulation of cells in the G_1 phase of the cell cycle. Retinoids inhibit chemical carcinogenesis in vivo in skin in inhibition can be augmented when retinoid treatment is combined with other chemopreventive modalities. For example, there is a synergistic effect in the inhibition of breast cancer in rats when retinoid treatment is combined either with ovariectomy or with treatment with bromocriptine, an inhibitor of prolactin secretion from the pituitary. Retinoids suppress malignant transformation in vitro whether the carcinogenic stimulus is a chemical carcinogen, ionizing radiation, or the sarcoma growth factor of the Moloney sarcoma virus. Retinoids inhibit tumor promotion and induction of ornithine decarboxylase by phorbol esters, but may also interfere with tumor initiation, since they inhibit carcinogen-induced aryl hydrocarbon hydroxylase and inhibit binding of carcinogen to DNA.

In this issue of the Journal, Levine describes a novel approach to the study of retinoid effects on melanoma. In this in vivo model system, Cloudman S91 murine melanoma cells are inoculated into upper dermal blister cavities created by negative suction pressure in the skin of DBA/2 mice. The resultant tumor nodules resemble cutaneous metastases of melanoma by virtue of their superficial dermal location. Topical applications of all-trans-retinoic acid at varying concentrations in DMSO, begun one day and continuing for 28 days after inoculation, prevents development of visible or palpable tumors and decreases incorporation of [\(^{14}\mathrm{C}\)]thymoacil, a measure of melanoma growth, in a dose-dependent manner. Most of the retinoid-treated animals had moderate erythema at sites of application indicating that the role of nonspecific inflammation as a possible cause of inhibition of tumor formation in this system requires further study.

Although it is more direct to study the mechanisms of action of retinoids in cell culture, this model system has potential utility in investigating the in vivo factors, such as host immune status, that may modulate the response to retinoid therapy. Additionally, this model for detecting antimelanoma activity could be of value as a secondary efficacy screen for many of the more than 1500 retinoids that have been synthesized to date and have shown activity in preliminary in vitro screens. This system could be easily modified to allow study of tumors other than melanoma. This report also emphasizes the need for further investigation of the effects of topical application of synthetic retinoids, which would include minimizing the development of systemic toxicity.

The preclinical screening systems that have been most regularly employed to test the efficacy of newly synthesized retinoids have been the mouse papilloma assay of Bollag and the hamster tracheal organ culture system of Sporn. In the former system mice are treated with the test retinoid after carcinogen exposure and observed for the appearance of skin tumors. In the latter system retinoids are tested for their ability to reverse the keratinization of the squamous metaplasia seen in the vitamin A-deficient hamster trachea. Whereas these screens have been predictive of efficacy in benign and malignant epithelial diseases, it is apparent that with the expanding spectrum of retinoid-responsive diseases additional screening systems are necessary. Exclusive reliance on one or two screens could result in the loss of a valuable retinoid that could be effective in nonepithelial diseases, such as melanoma, myelodysplastic syndromes, and rheumatoid arthritis.

Perhaps even more critical to the future of retinoids is the placement of higher priority on screening new derivatives for acute and chronic toxicity than for efficacy. It would be a major advance, indeed, if new retinoids were found to be equal in efficacy to existing agents but markedly less toxic. In fact, some of the more recently synthesized retinoids lack the systemic toxicities that are so well known for isotretinoin and etretinate, such as alterations in liver function tests and serum lipids, teratogenicity, and bony toxicity.

Thus, the future of the retinoids appears most promising, particularly with the expanding spectrum of retinoid-responsive diseases beyond the familiar triad of acne, psoriasis, and cutaneous disorders of keratinization, and with the continuing development of new synthetic compounds that may improve still further their efficacy, but more importantly, their tolerability.

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REFERENCES

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